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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appl. No.	:	09/921,045	Confirmation No.: 7635
Applicant	:	David Dorris, et al.	
Filed	:	August 2, 2001	
TC/A.U.	:	1631	
Examiner	:	Cheyne D. Ly	
Docket No.	:	PU01111	
Customer No.	:	22840	

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

November 12, 2004

APPEAL BRIEF

Sir:

Appellants submit this Appeal Brief in triplicate, appealing from the June 14, 2004, rejection of the Primary Examiner, finally rejecting claims 1-3, 5, 16-18, 20 and 23-50 in the captioned application. The Notice of Appeal was filed on September 17, 2004.

Real Party in Interest

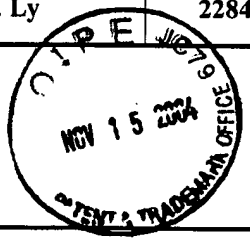
Amersham Biosciences AB, formerly known as Amersham Pharmacia Biotech AB, the assignee and owner of the captioned application, is the real party in interest to this appeal.

TRANSMITTAL OF APPEAL BRIEF (Large Entity)	Docket No. PU01111

In Re Application Of: **David Dorris, et al.**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/921,045	August 2, 2001	Cheyne D. Ly	22840	1631	7635

Invention: **Ratio-Based Oligonucleotide Probe Selection**



COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on **September 17, 2004.**

The fee for filing this Appeal Brief is: **$340.00**

- ☐ A check in the amount of the fee is enclosed.
- ☒ The Director has already been authorized to charge fees in this application to a Deposit Account.
- ☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **502-590.**
- ☐ Payment by credit card. Form PTO-2038 is attached.

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Signature

Dated: **November 12, 2004**

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Signature of Person Mailing Correspondence

Melissa Leck

Typed or Printed Name of Person Mailing Correspondence

cc:

Related Appeals and Interferences

There are no other appeals or interferences related to the instant appeal.

Status of Claims

Claims 1-67 are pending in the captioned application. Claims 4, 6-15, 19, 21, 22, and 51-67 have been withdrawn from consideration. The claims currently under examination, namely claims 1-3, 5, 16-18, 20 and 23-50 are appended hereto.

Status of Amendments

There are no outstanding amendments with regard to the captioned application.

Summary of Invention

This invention provides methods of choosing probes to a target sequence (*e.g.*, a gene), particularly probes for use in high-density oligonucleotide arrays. Because the present method provides for probes that allow for the accurate determination of the amount of target sequence within a composition over a wide range of concentrations, the use of multiple probes per gene may be obviated. Thus, such probes are useful in methods of accurately analyzing the expression of a gene within a cell or group of cells using only a single probe. The present invention also provides oligonucleotide arrays comprising such probes that are useful for accurately analyzing, at the same time, the expression. The claims are directed to embodiments of the methodology.

Issues

1. Whether claims 17, 18, 20, and 23-28 are properly rejected under 35 U.S.C. § 112, second paragraph.
2. Whether claims1-3, 5, 16-18, 20 and 23-50 are properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Manduchi et al. (2000) taken with Allzadeh et al. (2000) in combination with Lockhart et al. (US Pat. No. 6,040,138).

Grouping of Claims

All of the rejected claims in the rejection appealed hereunder stand or fall together.

Arguments

1. Claims 17, 18, 20, and 23-28 are not properly rejected under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 17, 18, 20 and 23–28 under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention".

Specifically, the Examiner stated, "specific to claims 17 and 23-28, line 2, the term 'complementary' causes the claim to be vague and indefinite because it is not clear what criteria are being used to determine that a nucleic acid sequence is complementary to another. Is a complement of 2 nucleotides of two different nucleotides sequence [sic.]

sufficient to consider said sequence complementary? Clarification of the metes and bounds is required. Claims 18 and 20 are rejected for being dependent from claim 17".

In response, Appellants respectfully asserted that the term "complimentary" is clear to one skilled in the art, and specifically directed the Examiner's attention to page 4, lines 4–11, wherein "complimentary" sequences are discussed. Inasmuch as claim 17 is dependent upon claim 1, which is directed to "a method of selecting a probe for a target nucleic acid sequence", Appellants respectfully asserted that requiring further metes and bounds is improper, as one skilled in the art could easily determine which probes are complimentary and which are not, and no metes and bounds are specifiable.

In response the Examiner stated that Appellants' arguments have "been fully considered and found to be unpersuasive", noting that the "pointed to support provides disclosure of one or more types of chemical bonds and recited 'Watson Crick base pairing' as an example" but continuing "said support does not provide criteria to which one of ordinary skill in the art may apply for determining a nucleic acid sequence being complementary to another sequence as specified by the elected claims".

In response, Appellants reiterate the arguments presented above and respectfully assert that one skilled in the art would readily comprehend what is meant by a complementary sequence, inasmuch as complementarity and pairing of bases (or which Watson Crick base pairing is a well recognized example) and/or modified bases is well recognized in the art. Appellants respectfully submit that the skill of the art is fairly advanced in this area, and that the skilled artisan would readily recognized what is and is not encompassed by the language the Examiner finds objectionable.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

2. Claims 1-3, 5, 16-18, 20 and 23-50 are not properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Manduchi et al. (2000) taken with Allzadeh et al. (2000) in combination with Lockhart et al. (US Pat. No. 6,040,138).

The Examiner has rejected claims 1–3,5, 16–18, 20, 23–50 under 35 U.S.C. § 103(a) as "being unpatentable over Manduchi et al. (2000) taken with Allzadeh et al. (2000) in combination with Lockhart et al. (US 6,040,138 A)".

Specifically, the Examiner stated, "Manduchi et al. discloses a method for selection of a probe on a microarray for a target nucleic acid sequence wherein two samples types (first composition and second composition) and the ratios from the two separate two-channel microarrays are compared using the same reference for one of the channels...For each homotypic group and for each gene tag, Manduchi et al. computes the average intensity of that tag over a plurality of samples in the group, sets the group in order, establishes a reference group to which other groups are compared, and lists the ratios..."

The Examiner continued, "up regulation is determined by comparing ratio r^1, of the average intensity of a gene tag at group I and the average intensity of the same gene tag at the reference group...The method of Manduchi et al. is applied to hybridizing 3 or more candidate probes...generating datasets containing five homotypic groups

comprising human blood progenitor cells..., as in instant claims 1, 3, 5, 20, 29, 31, and 40-50".

The Examiner further continued, "it is noted Manduchi et al. discloses a method directed to highly parallel gene expression experiments,...Although Manduchi et al. demonstrates said method with data generated from a two-channel microarray, said method is applicable to many types of data generated from highly parallel hybridization array experiments. It is well know in the art that a type of highly parallel hybridization array experiment is oligonucleotide arrays wherein gene expression is detected by the complementary of probe sequence to target sequence. The inclusion of a reference by Lipshutz et al. is not being used as prior art but to expand on what is well known in the art of parallel hybridization array experiments...Further, the inclusion of the Duggan et al. reference is not being used as prior art but to expand on what is well known in the art of parallel hybridization array experiments..."

The Examiner conceded, "Manduchi et al....does not disclose the limitations of claims 2, 30, and 32-37". However, the Examiner stated, "Allzadeh et al. discloses a method of generating said data by hybridizing select gene probes on a 'lymphochip' (first partner) to labeled targets from a cDNA libraries (second partner comprises a label)..." Further, the Examiner states, "the samples for microarray analysis disclosed by Allzadeh et al. comprises a low and high concentration and samples are treated in such growth conditions as phorbol ester, ionomycin, or anthracycline..."

The Examiner further conceded, "Manduchi et al. and Allzadeh et al. do not disclose the limitation wherein the first or second binding partner comprises biotin". The Examiner continued, "Lockhart et al. discloses the use of labels such as biotin for nucleic

acids (probe or target) in expression monitoring by hybridization to high-density oligonucleotide arrays...Lockhart et al. suggested an improvement for monitoring gene expression via hybridization arrays by using a rapid and effective method for identifying a set of oligonucleotide probes that maximized specific hybridization efficacy....The improvement suggested by Lockhart et al. is directly applicable to the method of parallel gene expression experiments via hybridization arrays..."

The Examiner concluded, "an artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement suggested by Lockhart et al. to perform a method of parallel gene expression experiments via hybridization arrays as taught by Manduchi et al. and Allzadeh et al. using biotin as taught by Lockhart et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to perform method of parallel gene expression experiments via hybridization arrays with biotin as taught by Manduchi et al., Allzadeh et al., and Lockhart et al.".

In response, Appellants respectfully submitted that the Examiner had misapplied the teachings of the base reference, Manduchi, et al., to the instant claimed invention. Specifically, as recited in claim 1, the invention encompasses a method for selecting a probe for a target nucleic acid molecule comprising seven steps. These steps include "hybridizing three or more candidate probes with a first composition comprising the target nucleic acid sequence; determining a first hybridization signal for each candidate probe; hybridizing the three or more candidate probes with a second composition comprising the target nucleic acid sequence; determining a second hybridization signal for each candidate probe; calculating a hybridization signal ratio of the first hybridization

signal to the second hybridization signal for each candidate probe; calculating an average hybridization signal ratio for the three or more candidate probes; and selecting the candidate probe by comparing a candidate probe's hybridization signal ratio to the average hybridization signal ratio".

Thus, Appellants summarized, the instant invention provides a process for identifying and selecting the best probe for a specific target nucleic acid sequence.

The Appellants further asserted that the Manduchi, et al. paper, on the other hand, discloses (in the abstract) a "protocol...to attach expression patterns to genes represented in a collection of hybridization array experiments", which method "reflects the broader change of focus in the field from studying a few genes with many replicates to studying many (possible thousands) of genes simultaneously, but with relatively few replicates. The approach of the instant differs from standard methods in that it exploits the fact that there are many genes in the arrays. These are used to estimate for each sample type an appropriate distribution that is employed to control false positives for each of the predictions made. Satisfactory results can be obtained using this method with as few as two replicates".

Thus, Appellants submitted, the Manduchi, et al. methodology exploits the fact that many assay determinations are being made in parallel, and such determinations may be made with many genes. Indeed, at page 686, column 2, the authors state, "our method exploits the fact that there are hundreds of genes to estimate the appropriate gene independent distribution within each sample type. By integrating over these distributions, false positive rates are calculated directly". The Appellants concluded that the Manduchi, et al. reference discloses a methodology whereby the distribution of

particular genetic markers, which may number many, can be determined among various cell types, further noting that there is no disclosure nor even any suggestion of a methodology to determine appropriate probes on the basis of the probes' hybridization signal ratio to the average hybridization signal ration of other probes for the same nucleic acid sequence.

Appellants further asserted that the addition of the Allzadeh article and the Lockhart, et al. patent do nothing to remedy this deficiency, specifically noting that the Lockhart, et al. patent is mentioned in the Background of Invention section of the captioned application at page, lines 15–22, wherein it is stated, "Lockhart *et al.*, ...describe...a method...in that...a number of candidate probes to a target sequence are tested to determine which probe provided the strongest signal". In an attempt to account for probes that show a high background signal even in the absence of the target, Lockhart *et al.* compare the probe signal to a signal obtained from a second probe constructed to contain a single mismatch with the target sequence. Only those probes having a signal that is a certain percentage over the signal obtained with the mismatch probe are used. Lockhart *et al.* describe using multiple probes for a given target sequence in an array to accurately determine the expression level of a gene over a range of concentrations".

However, as stated in the captioned application at lines 25, et. seq., "ideally an array would contain only one probe of each gene yet would still be able to provide accurate differential gene expression profiles. Because a probe giving the highest hybridization signal in the given concentration of intended target (chosen by rapid prototyping) [such as in Lockhart, et al.] may not always provide for accurate gene expression profiles wherein different samples having varying amounts or varying

structures of the intended target, there is a need for arrays containing only a single probe to each gene yet are still able to indicate variation in the expression level of the gene".

Regarding the Allzadeh, et al. reference, Appellants asserted that there is similarly no disclosure or even any suggestion of the instant invention. Indeed, while Applicants concede that the Allzadeh, et al. article discloses gene expression profiling, such is quite different from the instant invention.

In response, the Examiner stated, "Claim 1 recites steps a) to g) for selecting a probe for a target nucleic acid; however, said claim does not recite [sic.] any limitations or methods or steps for determining the "best" or "appropriate probes". While Appellants do concede that these words are not used, Appellants also point out that the purpose of running multiple candidate probes in the claim is to determine which probe produces the desirable signal as compared with the average signal (see e.g. g) of Claim 1); indeed, there would be little reason to run the multiple if one were not comparing their performance of them. And this is neither disclosed, nor even suggested, by the combination of references set forth by the Examiner.

In response, the Examiner noted that Manduchi et al. discloses a method "wherein two sample types (first composition and second composition) and the ratios from the two separate-two channel microarrays are compared using the same reference for the channels ... For each homotypic group and each gene tag Manduchi et al. computes the average intensity of the tag over a plurality of samples in the group, sets the groups in order, establishes a reference group to which the other groups are compared, and lists the ratios". The Examiner continued, "Up regulation is determined by comparing the ratio of the average intensity of a gene tag at group I and the average intensity of the same tag

at the reference group ... The reiterated dictation of Maduchi et al above is consistent with the limitations of steps a) to g) of claim 1".

The Examiner further states, "Specific to the argument that Manduchi et al. does not disclose or suggest a method for determining 'the best' or 'appropriate' probes ... said claim does not recites [sic.] any [such] limitations or steps".

In response, Appellants reiterate the argument presented above and specifically point out that step g) of claim 1 specifically requires selection of the ultimate probe for the nucleic acid sequence, "by comparing a candidate probe's hybridization signal to the average hybridization signal". Appellants respectfully assert that it is implicit in the claim that the probe selected by the methodology will be the best, or the appropriate probe for the nucleic acid sequence; otherwise, Appellants respectfully submit, the process would have no useful purpose.

Further, with regard to the Allzadeh and Lockhart et al. references, the Examiner states that the "combination of Manduchi et al., Allzadeh et al. has been directed to the limitations [of] claims 2, 30, and 32-37". The Examiner further cites a reference to Duggan et al. (Nature Genetics Supplement, 21, pp 10-14, January 1999) "to expand on what is known in the art of parallel hybridization" and specifically, the use of "cDNA microarrays wherein fluorescent tagged transcripts are, on average, 600 bp, have an average of 2 fluorescent tags per 100 bp and hybridize, all of the (contiguous) to their probe, and also cites a reference to Lipschutz et al. (Nature Genetics Supplement, 21, pp 20-24, January 1999) "to expand on what is known in the art of parallel hybridization" and further "wherein [a complementary] sequence is complementary to at least 15

contiguous nucleotides in the target sequence". The Examiner specifically states that the inclusion of each of these references "is not being used as prior art".

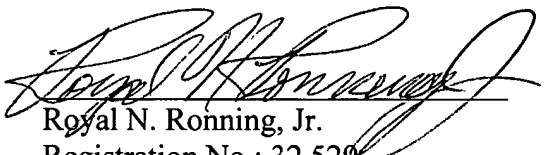
In response, Appellants reiterate the arguments presented above and respectfully assert that the inclusion of the Allazadeh and Lockhart et al. references, as well as the Duggan et al. and Lipschutz et al references ("not being used as prior art") do nothing to remedy the deficiencies of the Manduchi et al. reference and that the references, taken alone and in combination with one another, neither disclose nor even suggest the instant invention.

In view of the foregoing, Appellants respectfully submit that the Examiner's rejection cannot be upheld and should be reversed.

Conclusion

In view of the foregoing arguments, Appellants respectfully assert that the Examiner's rejections presented above cannot be sustained, and should be reversed.

Respectfully submitted,



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Signature: 

Name: Melissa Leck

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APPENDIX A

The Rejected Claims

Claim 1 (original): A method of selecting a probe for a target nucleic acid sequence, the method comprising the steps of:

a) hybridizing three or more candidate probes with a first composition comprising the target nucleic acid sequence;

b) determining a first hybridization signal for each candidate probe;

c) hybridizing the three or more candidate probes with a second composition comprising the target nucleic acid sequence;

d) determining a second hybridization signal for each candidate probe;

e) calculating a hybridization signal ratio of the first hybridization signal to the second hybridization signal for each candidate probe;

f) calculating an average hybridization signal ratio for the three or more candidate probes; and

g) selecting the candidate probe by comparing a candidate probe's hybridization signal ratio to the average hybridization signal ratio.

Claim 2 (original): The method of claim 1, wherein the target nucleic acid comprises cDNA.

Claim 3 (original): The method of claim 2, wherein the cDNA is derived from a mammalian cell.

Claim 4 (withdrawn): The method of claim 3, wherein the mammalian cell is a rat cell.

Claim 5 (original): The method of claim 3, wherein the mammalian cell is a human cell.

Claim 6 (withdrawn): The method of claim 1, wherein the target nucleic acid comprises genomic DNA.

Claim 7 (withdrawn): The method of claim 6, wherein the genomic DNA is derived from a mammalian cell.

Claim 8 (withdrawn): The method of claim 7, wherein the mammalian cell is a rat cell.

Claim 9 (withdrawn): The method of claim 7, wherein the mammalian cell is a human cell.

Claim 10 (withdrawn): The method of claim 1, wherein the target nucleic acid comprises RNA.

Claim 11 (withdrawn): The method of claim 10, wherein the RNA is derived from a mammalian cell.

Claim 12 (withdrawn): The method of claim 11, wherein the mammalian cell is a rat cell.

Claim 13 (withdrawn): The method of claim 11, wherein the mammalian cell is a human cell.

Claim 14 (withdrawn): The method of claim 1, wherein the target nucleic acid is derived from a prokaryote.

Claim 15 (withdrawn): The method of claim 1, wherein the target nucleic acid is derived from a virus.

Claim 16 (original): The method of claim 1, wherein the three or more candidate probes comprise a nucleic acid sequence complementary to the target sequence.

Claim 17 (original): The method of claim 1, wherein the three or more candidate probes comprise a nucleic acid sequence complementary to an expressed sequence or the expressed sequence's complement.

Claim 18 (original): The method of claim 17, wherein the expressed sequence comprises a mammalian expressed sequence.

Claim 19 (withdrawn): The method of claim 18, wherein the mammalian expressed sequence is a rat expressed sequence.

Claim 20 (original): The method of claim 18, wherein the mammalian expressed sequence is a human expressed sequence.

Claim 21 (withdrawn): The method of claim 1, wherein the three or more candidate probes comprise a nucleic acid sequence complementary to a genomic nucleic acid sequence.

Claim 22 (withdrawn): The method of claim 1, wherein the three or more candidate probes comprise a nucleic acid sequence complementary to a viral nucleic acid sequence or the viral nucleic acid sequence's complement.

Claim 23 (original): The method of claim 1, wherein the three or more candidate probes comprise a candidate probe comprising a nucleic acid sequence complementary to at least 15 contiguous nucleotides of the target sequence.

Claim 24 (original): The method of claim 23, wherein each of the three or more candidate probes comprise a nucleic acid sequence complementary to at least 15 contiguous nucleotides of the target sequence.

Claim 25 (original): The method of claim 1, wherein the three or more candidate probes comprise a candidate probe comprising a nucleic acid sequence complementary to at least 30 contiguous nucleotides of the target sequence.

Claim 26 (original): The method of claim 25, wherein each of the three or more candidate probes comprise a nucleic acid sequence complementary to at least 30 contiguous nucleotides of the target sequence.

Claim 27 (original): The method of claim 23, wherein the three or more candidate probes comprise a candidate probe comprising a nucleic acid sequence complementary to less than 100 contiguous nucleotides of the target sequence.

Claim 28 (original): The method of claim 25, wherein the three or more candidate probes comprise a candidate probe comprising a nucleic acid sequence complementary to less than 100 contiguous nucleotides of the target sequence.

Claim 29 (original): The method of claim 1, wherein a nucleic acid array comprises the three or more candidate probes.

Claim 30 (original): The method of claim 1, wherein the first composition and the second composition comprise a concentration of the target sequence, the concentration within the first composition differing from the concentration within the second composition.

Claim 31 (original): The method of claim 30, wherein the first composition is derived from a different tissue type from that in which the second composition is derived.

Claim 32 (original): The method of claim 30, wherein the first composition and the second composition are derived from a cell type grown at growth conditions, the growth conditions from which the first composition is derived differing from the growth conditions from which the second composition is derived.

Claim 33 (original): The method of claim 30, wherein the first composition and the second composition comprise different concentrations of a stock composition derived from one or more cells.

Claim 34 (original): The method of claim 1, wherein the hybridizing comprises stringent conditions.

Claim 35 (original): The method of claim 1, wherein the target nucleic acid comprises a detectable moiety.

Claim 36 (original): The method of claim 1, wherein the target nucleic acid comprises a first partner of a binding pair.

Claim 37 (original): The method of claim 36, wherein a second partner of the binding pair comprises a label.

Claim 38 (original): The method of claim 36, wherein the first partner comprises biotin.

Claim 39 (original): The method of claim 37, wherein the second partner comprises biotin.

Claim 40 (original): The method of claim 1, wherein determining a first hybridization signal comprises averaging more than one hybridization signal for the candidate probe hybridized with the first composition.

Claim 41 (original): The method of claim 1, wherein determining a second hybridization signal comprises averaging more than one hybridization signal for the candidate probe hybridized with the second composition.

Claim 42 (original): The method of claim 1, further comprising the steps of:

c1) hybridizing the three or more candidate probes with a third composition comprising the target nucleic acid sequence;

d1) determining a third hybridization signal for each candidate probe;

e1) calculating a second hybridization signal ratio of the first hybridization signal to the third hybridization signal for each candidate probe;

f1) calculating an average second hybridization signal ratio for the three or more candidate probes; and

g1) selecting the candidate probe by comparing a candidate probe's second hybridization signal ratio to the average second hybridization signal ratio

Claim 43 (original): The method of claim 42, wherein the selecting comprises selecting the candidate probe by comparing the candidate probe's hybridization signal ratio and second hybridization signal ratio to the average hybridization signal ratio and average second hybridization signal ratio.

Claim 44 (original): The method of claim 42, further comprising the steps of:

e2) calculating a third hybridization signal ratio of the second hybridization signal to the third hybridization signal for each candidate probe; and

f2) calculating an average third hybridization signal ratio for the three or more candidate probes.

Claim 45 (original): The method of claim 44, wherein the selecting comprises selecting the candidate probe by comparing the candidate probe's hybridization signal ratio, second hybridization signal ratio, and third hybridization signal ratio to the average hybridization signal ratio, average second hybridization signal ratio, and average third hybridization signal ratio.

Claim 46 (original): The method of claim 1, wherein selecting comprises selecting the candidate probe having a hybridization signal ratio closest to the average hybridization signal ratio.

Claim 47 (original): The method of claim 42, wherein selecting comprises selecting the candidate probe having a second hybridization signal ratio closest to the average second hybridization signal ratio.

Claim 48 (original): The method of claim 43, wherein the selecting comprises selecting the candidate probe having a hybridization signal ratio and second hybridization signal ratio closest to the average hybridization signal ratio and average second hybridization signal ratio.

Claim 49 (original): The method of claim 45, wherein the selecting comprises selecting the candidate probe having a hybridization signal ratio, second hybridization signal ratio, and third hybridization signal ratio closest to the average hybridization signal ratio, average second hybridization signal ratio, and average third hybridization signal ratio.

Claim 50 (original): The method of claim 1, wherein the first composition comprises a first concentration of the target nucleic acid sequence and the second composition comprises a second concentration of the target nucleic acid sequence, the method comprising:

alternatively to step f), a step of calculating a concentration ratio of the first concentration of the target nucleic acid to the second concentration of the target nucleic acid; and

alternatively to step g), selecting the candidate probe by comparing the candidate probe's hybridization signal ratio to the concentration ratio.

Claim 51 (withdrawn): The method of claim 66, wherein the selecting comprises selecting the candidate probe having a hybridization signal ratio closest to the concentration ratio.

Claim 52 (withdrawn): A method of making an oligonucleotide array, comprising the steps of:

a) hybridizing three or more candidate probes comprising a nucleic acid sequence with a first composition comprising the target nucleic acid sequence;

b) determining a first hybridization signal for each candidate probe;

c) hybridizing the three or more candidate probes with a second composition comprising the target nucleic acid sequence;

d) determining a second hybridization signal for each candidate probe;

e) calculating a hybridization signal ratio of the first hybridization signal to the second hybridization signal for each candidate probe;

f) calculating an average hybridization signal ratio for the three or more candidate probes;

g) selecting the candidate probe by comparing the candidate probe's hybridization signal ratio to the average hybridization signal ratio, yielding a first probe; and

h) constructing an oligonucleotide array comprising a probe comprising the nucleic acid sequence of the first probe.

Claim 53 (withdrawn): The method of claim 52, wherein steps a) through g) are repeated with a second target sequence and second candidate probes to yield a second probe and constructing a nucleic acid array comprising the first probe and the second probe.

Claim 54 (withdrawn): The method of claim 52, wherein selecting comprises selecting the candidate probe having a hybridization signal ratio closest to the average hybridization signal ratio.

Claim 55 (withdrawn): An oligonucleotide array comprising at least 10 probes to 10 different human genes, the probes selected using the method of claim 1.

Claim 56 (withdrawn): The oligonucleotide array of claim 55 comprising at least 100 probes to 100 different human genes, the probes selected using the method of claim 1.

Claim 57 (withdrawn): The oligonucleotide array of claim 56 comprising at least 1000 probes to 1000 different human genes, the probes selected using the method of claim 1.

Claim 58 (withdrawn): The oligonucleotide array of claim 57 comprising at least 5000 probes to 5000 different human genes, the probes selected using the method of claim 1.

Claim 59 (withdrawn): The oligonucleotide array of claim 58 comprising at least 10000 probes to 10000 different human genes, the probes selected using the method of claim 1.

Claim 60 (withdrawn): The oligonucleotide array of claim 55, wherein every probe of the array represents a different gene.

Claim 61 (withdrawn): The oligonucleotide array of claim 58 wherein every probe of the array represents a different gene.

Claim 62 (withdrawn): A method of analyzing the expression of a gene within a source, comprising:

a) hybridizing a nucleic acid composition derived from the source with the oligonucleotide array of claim 47 comprising a probe representing the gene; and

b) determining hybridization of a nucleic acid within the composition to the probe representing the gene, wherein hybridization of a nucleic acid within the composition to the probe representing the gene indicates expression of the gene within the source.

Claim 63 (withdrawn): The method of claim 62, wherein the expression of at least 10 genes is analyzed.

Claim 64 (withdrawn): The method of claim 63, wherein the expression of at least 100 genes is analyzed.

Claim 65 (withdrawn): The method of claim 64, wherein the expression of at least 1000 genes is analyzed.

Claim 66 (withdrawn): The method of claim 65, wherein the expression of at least 5000 genes is analyzed.

Claim 67 (withdrawn): The method of claim 66, wherein the expression of at least 10000 genes is analyzed.